REMARKS

Included herewith is a petition for a one-month extension of time with instructions to charge the required fee to an appropriate deposit account. The time for response is now set to expire on October 19, 2001.

Claim 4 stands rejected under 35 U.S.C.§112, first paragraph. It was stated in the first Office Action of November 21, 2000 that "No antibodies or constructs capable of binding with both the CD3 ε and γ chains are disclosed." Applicants reiterate their argument made in the previous amendment of April 9, 2001 that UCHT-1 binds to both the ε and γ chains of CD3. In the previously submitted paper by A. Salmeron et al., J. of Immunol., 147(9), pp. 3047-52, 1991 it is shown that UCHT-1 binds to both CD3-ε and CD3-γ. In particular, in the last sentence of the last full paragraph in column 2 of page 3048, it is stated:

> Taken together, these results showed that UCHT-1 and Leu-4 recognized the complexes of CD3-ε with CD3-γ ...

The above passage demonstrates that it is known in the prior art that UCHT-1 recognizes both CD3-ε and CD3-γ chains, therefore, this rejection of Claim 4 is in error and should be withdrawn.

New grounds of rejection under 35 U.S.C.§112, first paragraph, have been included in the Final Rejection of June 19, 2001. Applicants have made certain amendments herein to overcome these grounds of rejection, or at the very least, to place the affected claims in better form for appeal.

Regarding the new matter rejection under 35 U.S.C.§112, first paragraph, it is stated on page 4 of the Final Rejection that "Claims 1-3, and 50" are rejected. It is believed that this was an inadvertent error and it was the Examiner's intention to cite "Claims 31-33". The remarks herein will be based on the assumption that Claims 31-33 were intended to be rejected; if this assumption is in error then applicants request the opportunity to respond again substantively.

Claims 31-33 have been amended to modify the phrases cited in the Final rejection as lacking support. Specifically, the language regarding "one or more" nucleotides in Claims 31 and 32 has been eliminated.

In Claim 33, the phrases "99% identical" and "95% as effective" have been replaced with, respectively, "90% identical" and "about 90% as effective". Support for this amendment is in original Claim 8 and on pages 21-22 of the specification. It is believed that this amendment renders the new matter rejection moot.

Claims 31-33 further stand rejected under 35 U.S.C.§112, first paragraph, for what is essentially insufficient written description. The Examiner contends that there is insufficient written description for nucleotides that hybridize to SEQ. ID. No. 2 and for antibodies having a variable region at least 99% (now at least 90%) identical to that of UCHT-1 and which is at least 95% (now at least about 90%) as effective on a molar basis in competing with UCHT-1. *University of California v.Eli Lilly and Co.*, 43 USPQ2d 1398, is cited to support this rejection.

It is respectfully submitted that the facts of *Eli Lilly* are wholly non-analogous to the facts in the present application. In *Eli Lilly* applicants were attempting to claim human cDNA without disclosing the sequence of the human cDNA. Furthermore, the applicants attempted to claim "vertebrate insulin cDNA" or "mammalian insulin cDNA" while disclosing only the sequence for rat insulin cDNA. In the present application, the rejected claims concern specific sequences (i.e., SEQ. ID. No. 2 and the known variable region of UCHT-1). The CAFC specifically held that the Applicants in *Eli Lilly* did "not define any structural features commonly possessed by members of the genus that distinguish them from others" (*Eli Lilly* at 1406) and, regarding the cDNA claims, that "there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics" (*Eli Lilly* at 1405).

In marked contrast to *Eli Lilly,* in the presently rejected claims, there is unambiguous sequence information and specific procedures for determining the scope of the invention from the sequences in the specification, i.e., specific descriptions of how to determine "identity" and "hybridization under stringent conditions". Thus, as opposed to *Eli Lilly*, applicants' claims define specific, tangible structural features possessed by members of the claimed genus that distinguishes them from others. One skilled in the art would have no trouble determining whether or not a specific construct is inside or outside the claim scope as written.

Moreover, there are innumerable issued U.S. patents using "identity" and "hybridizing" language similar to the present language which demonstrates that the U.S. P.T.O. has held such language to meet the requirements of 35 U.S.C.§112.

Claims 1-16 and 29-35 stand rejected under 35 U.S.C.§103(a) as being unpatentable over U.S. Patent No. 6,103,735 in view of Thompson et al. and Kreitman et al. or U.S. Patent No. 5,489,525.

It is again submitted that there is not sufficient motivation to combine the references to arrive at applicants' invention to render such invention obvious within the meaning of 35 U.S.C.§103(a). As is well settled, "obvious to try" is not the standard for determining obviousness under 35 U.S.C.§103. Both the suggestion and the expectation of success must be found in the prior art, not in applicant's disclosure (*In re Dow Chemical Co.* 5 USPQ2d 1529). There is no explicit suggestion in any of the cited references to construct an immunotoxin comprising an anti-CD3 antibody and a Pseudomonas A exotoxin ("PE").

The Examiner points out that it was known from Thompson et al. that DT immunotoxins are problematic in human treatment due to antibodies already present. However, Thompson et al. solves this "problem" by truncating the DT toxin to eliminate or drastically reduce the antibody response. Therefore, why would one skilled in the art be motivated to modify Thompson et al., or combine Thompson et al. with another reference, where Thompson et al. has already solved the "problem"? The answer is that one skilled in the art would not be so motivated. The bits and pieces of applicants' invention may be present in the various prior art documents, however, what is missing is the requisite motivation to extract the bits and pieces and combine them to arrive at applicants' invention.

Furthermore, *a priori*, one could not predict the effectiveness of applicants' claimed invention, i.e., one skilled in the art would not have a reasonable expectation of success. Thompson et al. equates immunotoxin constructs having ricin with those having PE. U.S. Patent No. 5,489,525 equates immunotoxins containing PE with those containing:

> diphtheria toxin, shiga toxin, and shiga-like toxin, and ribosome inactivating toxins derived from plants and fungi, including ricin, α-sarcin, restrictotocin, mitogellin, tricanthosin, saporin-G, saporin-1, momordin, gelonin, pokeweed antiviral protein, abrin, modecicin and others...; and recombinant derivatives of those proteins...mammalian derived (preferably human) proteins with ribonucleolytic activity, such as ribonucleases engineered to be potent cytotoxins, and mammalian derived angiogenin...(see lines 17-37 of column 8).

A skilled artisan could not predict the effectiveness of a particular combination without actually evaluating such combination because of the variables know to affect the activities of recombinant immunotoxins such as the size, shape, etc of the immunotoxin; number of receptors on the target cells; affinity of the immunotoxin for the receptor; intracellular routing and processing, and a host of other factors. Following the reasoning of the rejection in the Office Action, one skilled in the art reading U.S. patent 5,489,525 would predict a CD3 immunotoxin containing ricin to be equivalent to one containing momordin, to be equivalent to one containing saporin-G, to be equivalent to one containing PE, etc. It is submitted that this is manifestly not the case.

Applicants note the correct title of reference AS. A copy of reference AQ is provided herewith with an additional Form PTO-1449 which cites reference AQ and three other references. The Examiner is requested to fully consider reference AQ and the others cited and appropriately initial the Form PTO-1449.

It is submitted that applicants' specification and claims are in proper form. Applicants respectfully request that the rejection of the claims under 35 U.S.C.§112 and 103(a) be withdrawn and that pending claims 1-7, 9-16, and 19-34 be passed to allowance.

Respectfully submitted,

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APPENDIX A

IN THE SPECIFICATION

On page 7 under "Brief Description of the Figures", the description of Figure 1 has been amended as follows:

FIG. 1 Schematic diagram showing domain organization of scFv (UCHT-1)-PE38 molecule (SEQ. ID. No. 1), prepared in Example 1, consisting of an N-terminal light chain variable region (V_L) of 109 residues, a peptide linker (L) of 16 residues (SEQ. ID. No. 5), a heavy chain variable region (V_H) of 122 amino acids, a connector segment (C) of 5 amino acids (KASGG) (SEQ. ID. No. 9), and the PE38 mutant, comprising 347 amino acids ("Toxin").

IN THE CLAIMS

Claims 31-33 have been amended as follows:

Claim 31 (amended). A recombinant immunotoxin polypeptide and the pharmaceutically acceptable salts thereof, wherein the polypeptide comprises the polypeptide encoded by [the one or more] a nucleotide [sequences] sequence which [hybridize] hybridizes to the nucleotide sequence of claim 30 (SEQ. ID. No. 2) under stringent hybridization conditions.

Claim 32 (amended). A recombinant immunotoxin polypeptide and the pharmaceutically acceptable salts thereof, wherein the polypeptide comprises the polypeptide encoded by any nucleotide sequence which hybridizes to [the] said [one or more] nucleotide [sequences] sequence of claim 31 under stringent hybridization conditions.

Claim 33 (amended). A recombinant immunotoxin polypeptide and pharmaceutically acceptable salts thereof according to claim 2, wherein the CD3-binding domain comprises the FV region, or a CD3-binding fragment thereof of an antibody selected from: monoclonal antibody UCHT-1, an antibody having a variable region which is at least [99] 90% identical to the variable region of UCHT-1 and is at least [95] about 90% as effective on a molar basis in competing with UCHT-1 for binding to human CD3 antigen and having at least one sequence segment of at least five amino acids of human origin.